primers might be desired for liquid primer solutions because of self-annealing properties of larger primers in solution. Dried primer kits were also known for use with 9-mer and higher primers. (Rediprime, EP 298,269 discloses 15-mers and 17-mers) These were not thought to be subject to the problem of Suganuma. Moreover, there still remained a bias preferring longer primers because of the belief that such longer primers would provide more rapid priming than shorter primers.

The present invention relates to the discovery that there is a self-annealing problem with dried primers and that the solution to that problem is the use of shorter dried primers. Accordingly, the invention is thus directed to dried mixtures of random primers and relates to the discovery that self-annealing occurs when random 9-mers are used in dried predispensed labeling kits. The problem is specific to 9-mers (and longer oligonucleotides) used in dried kits and does not represent a problem with shorter dried primers.

II. The Outstanding Rejections

Claims 1 and 3-5 are rejected under 35 U.S.C. 103(a) over Godiska et al., U.S. 5,759,804 in view of Shen et al., EP 0 726 310 A1.

Claim 6 stands rejected under 35 U.S.C. 103(a) over Godiska et al., U.S. 5,759,804 in view of Shen et al., EP 0 726 310 A1 in further view of Hoeltke et al., U.S. 5,814,502.

III. The Rejections Under 35 U.S.C. 103(a) Should be Withdrawn.

The Obviousness rejections under 35 U.S.C. §103(a) should be withdrawn because (1) the selection of 6-mers to 8-mers does constitutes a critical range (see the application examples) and (2) the art fails to suggest that short primers (6-8 mers) would be desirable in a dried primer system. Thus, Applicant's examples demonstrate a critical difference in self-priming activity and labeling intensity between 6-8 mers and 9-mers.

More specifically, there is nothing in Godiska that teaches (1) that the selection of 6-mers to 8-mers constitutes a critical range (see the application examples) and (2) that short primers (6-8 mers) would be desirable in a dried primer system. While Godiska discloses a random

mixture of 6-mers and other ingredients the Examiner acknowledges that Godiska does not teach a labeling composition in a dry state. Moreover, there is nothing in Godiska that teaches that the selection of 6-mers to 8-mers is important in either the liquid or freeze dried state to reduce self-annealing. In fact, self annealing is not mentioned at all!

In addition, Shen, which discloses 48-mer and 22-mer primers (Example 1 and SEQ ID NOS 1 and 2) fails to suggest that dried primers should be shortened or alternatively any reason why the primers of Godiska should be dried. This is because the prior art generally taught that longer primers were preferred because longer primers have higher melting temperatures and are thus more specific.

Moreover, Shen acknowledges that "whether a particular composition will function to preserve biological activity for a particular biologically active material is not a priori predictable" (page 4, lines 36-37) and only discloses freeze-drying as an "option" (pg 5, lines 14-15) and In addition, Shen fails to provide any reason why the primers of Godiska should be dried given the fact that shorter primers were thought to be inherently more stable and there was no reason to believe that the shorter Godiska primers would benefit from being in freeze-dried kits.

Finally, Hoeltke does nothing to make up for the deficiencies of Godiska and Shen with respect to teaching the subject matter of independent claim 1. While it teaches that optimum detergent concentrations vary for different primer lengths it does not teach that 6-8 mers would be preferred to longer oligonucleotides in a dried reagent system.

For these reasons, the rejections under 35 U.S.C. §103 (a) should properly be withdrawn and each of claims 1 and 3-6 should be allowed. Should the Examiner have any questions or comments of form on substance, she is encouraged to contact the undersigned attorney.

Respectfully submitted,

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